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(54) Title: COMPOSITIONS AND METHODS FOR TREATING BENIGN PROSTATIC HYPERTROPHY

(57) Abstract

Invented are pharmaceutical compositions containing N-t-butyl-androst-3,5-diene-17β-carboxamide)-3-carboxylic acid or a salt thereof or 17β-(N-t-butylcarboxamide-estra-1,3,5(10)-triene-3-carboxylic acid or a salt thereof and an alpha-adrenergic receptor antagonist compound, and methods of using these compositions to treat benign prostatic hypertrophy.

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Compositions and Methods For Treating Benign Prostatic Hypertrophy

This invention relates to a pharmaceutical composition containing N-t-butyl-androst-3,5-diene-17ß-carboxamide-3-carboxylic acid or a salt thereof or 17ß-(N-t-butylcarboxamide)-estra-1,3,5(10)-triene-3-carboxylic acid or a salt thereof and an alpha-andrenergic receptor antagonist compound and a pharmaceutically acceptable carrier or diluent. This invention also relates to a method of treating benign prostatic hypertrophy in a mammal, including a human, in need thereof which comprises administering an effective dose of N-t-butyl-androst-3,5-diene-17ß-carboxamide-3-carboxylic acid or a salt thereof or 17ß-(N-t-butylcarboxamide-estra-1,3,5(10)-triene-3-carboxylic acid or a salt thereof and an alpha-andrenergic receptor antagonist compound to such mammal.

BACKGROUND OF THE INVENTION

As one of the primary regulators of peripheral vascular tone, α adrenoceptors long have been the targets of efforts to develop agents effective in changing vascular tone for use in treating diseases, such as hypertension, in which alterations in vascular resistance produce therapeutic benefits.

Lafferty, et al. U.S. Patent No. 4,963,547 (hereinafter Lafferty I) discloses that compounds which are alpha-andrenergic receptor antagonists are useful in treating cardiovascular diseases in which changes in vascular resistance are desirable, including hypertension, pulmonary hypertension, congestive heart failure, myocardial ischemia, angina pectoris, and peripheral vascular disease.

Lafferty I also discloses that said compounds are useful in treating vascular disorders such as diabetes, benign prostatic hypertrophy and ocular hypertension.

Lafferty I does not disclose that compounds which are alpha-andrenergic receptor antagonists as having utility in combination with an inhibitor of steroid 5-α-reductase.

N-t-butyl-androst-3,5-diene17ß-carboxamide-3-carboxylic acid and salts thereof (hereinafter Compound A) is disclosed and claimed in Holt, et al. U.S. Patent No. 5,017,568 (Holt I).

Holt I discloses Compound A as a novel steroid 5-α-reductase inhibiting compound which exhibits the therapeutic effect of lowering prostatic levels of dihydrotestosterone thereby reducing prostate size.

All of the compounds disclosed in Holt I as having 5-α-reductase inhibiting activity have utility in the invented compositions.

Holt I does not disclose compound A in combination with an alpha-andrenergic receptor antagonist compound.

17ß-(N-t-butylcarboxamide)-estra-1,3,5(10)-triene-3-carboxylic acid and salts thereof (hereinafter Compound B) is disclosed and claimed in Holt et al. U.S. Patent No. 4,954,446 (Holt II).

Holt II discloses compound B as a novel steroid 5-α-reductase inhibiting compound which exhibits the therapeutic effect of lowering prostatic levels of dihydrotestosterone thereby reducing prostate size.

All of the compounds disclosed in Holt II as having 5-α-reductase inhibiting activity have utility in the invented compositions.

Holt II does not disclose compound B as having utility in combination with an alpha-andrenergic receptor antagonist compound.

SUMMARY OF THE INVENTION

This invention relates to a pharmaceutical composition containing N-t-butyl-androst-3,5-diene-17ß-carboxamide-3-carboxylic acid or a salt thereof or 17ß-(N-t-butylcarboxamide)-estra-1,3,5(10)-triene-3-carboxylic acid or a salt thereof and an alpha-andrenergic receptor antagonist compound and a pharmaceutically acceptable carrier or diluent. This invention also relates to a method of treating benign prostatic hypertrophy in a mammal, including a human, in need thereof which comprises administering an effective dose of N-t-butyl-androst-3,5-diene-17ß-carboxamide-3-carboxylic acid or a salt thereof or 17ß-(N-t-

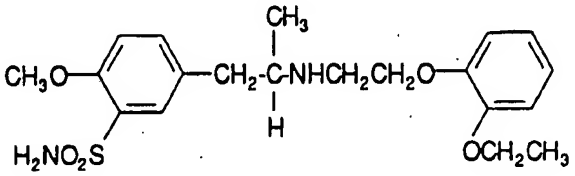
butylcarboxamide)-estra-1,3,5(10)-triene-3-carboxylic acid or a salt thereof and an alpha-andrenergic receptor antagonist compound to such mammal.

DETAILED DESCRIPTION OF THE INVENTION

Compounds which are alpha-andrenergic receptor antagonists are disclosed in Lafferty I as representing a well known therapeutic class of compounds.

Preferred alpha-andrenergic receptor antagonists for use in the compositions and methods of the invention include amsulosin, terazocin, doxazosin, alfuzosin, indoramin and prazosin and 7-chloro-2-ethyl-3,4,5,6-tetrahydro-4-methylthieno[4,3,2-ef]-[3]benzazepine.

By the term "amsulosin" as used herein is meant a compound of the formula

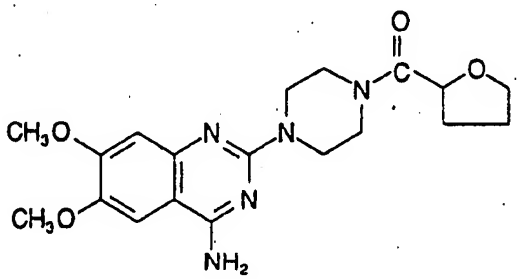


and salts, hydrates and solvates thereof.

Chemically, amsulosin is designated as (-)-(R)-5-[2-[[2-(O-ethoxyphenoxy)ethyl]amino]propyl]-2-methoxybenzenesulfonamide.

Amsulosin is disclosed in U.S. Patent Number 4,703,063 and claimed in U.S. Patent Number 4,987,125 as being useful in treating lower urinary tract dysfunction.

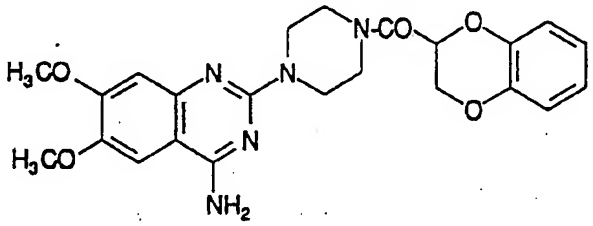
By the term "terazocin" as used herein is meant a compound of the formula



and salts, hydrates and solvates thereof.

Chemically, terazocin is designated as 1-(4-amino-6,7-dimethoxy-2 quinazolinyl)-4-[(tetrahydro-2-furoyl)carbonyl]piperazine. Terazocin is disclosed in U.S. Patent Number 4,251,532.

By the term doxazosin as used herein is meant a compound of the formula

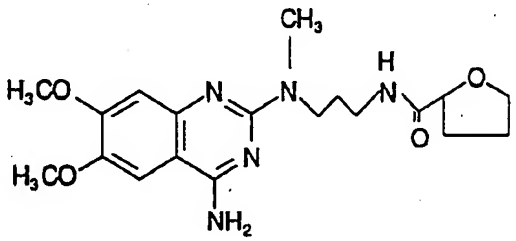


and salts, hydrates and solvates thereof.

Chemically "doxazosin" is designated as 1-(4-amino-6,7-dimethoxy-2-quinazolinyl)-4-[(2,3-dihydro-1,4-benzodioxin-2-yl)carbonyl]-piperazine.

Doxazosin is discolsed in U.S. Patent Number 4,188,390.

By the term "alfuzosin" as used herein is meant a compound of the formula

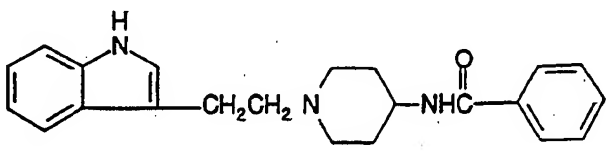


and salts, hydrates and solvates thereof.

Chemically alfuzosin is designated as N-[3-[(4-amino-6,7-dimethoxy-2-quinazolinyl)methylamino]propyl]tetrahydro-2-furancarboxamide.

Alfuzosin is disclosed in U.S. Patent Number 4,315,007.

By the term "indoramin" as used herein is meant a compound fo the formula

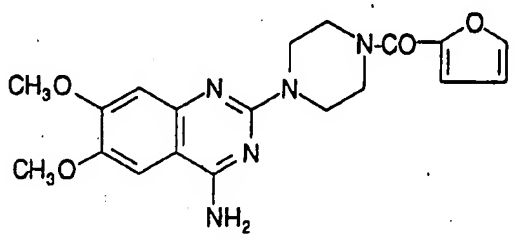


and salts, hydrates and solvates thereof.

Chemically indoramin as designated N-[[1-[2-(1H-indol-3-yl)ethyl]-4-piperidinyl]benzamine.

Indoramin is disclosed in U.S. Patent Number 3,527,761.

By the term "prazosin" as used herein is meant a compound of the formula



and salts, hydrates and solvates thereof.

Chemically prazosin is designated as 1-(4-amino-6,7-dimethoxy-2-quinazolinyl)-4-(2-furanylcarbonyl)piperazine.

Prazosin is disclosed in U.S. Patent Number 3,511,836.

The term "7-chloro-2-ethyl-3,4,5,6-tetrahydro-4-methylthieno[4,3,2-ef]-[3]benzazepine" as used herein includes salts, hydrates and soluates thereof. 7-chloro-2-ethyl-3,4,5,6-tetrahydro-4-methylthieno[4,3,2-ef]-[3]benzazepine is disclosed in U.S. patent number 5,006,521. Additionally, all compounds disclosed in U.S. patent number 5,006,521 as alpha-andrenergic receptor antagonist are preferred alpha-andrenergic receptor antagonist as used herein.

Persons skilled in the art can readily determine if a compound other than one specifically referred to herein is a alpha-andrenergic receptor antagonist by utilizing the assay described in Lafferty I. Thus, all such compounds are included within the scope of the term "alpha-andrenergic receptor antagonist" as used herein.

By the term "administering" as used herein is meant either simultaneous administration or any manner of consecutive administration of compound A or compound B and an alpha-andrenergic receptor antagonist compound. Preferably, if the administration is not simultaneous, the two compounds are administered in a close time proximity to each other. Furthermore, it does not matter if the compounds are both administered in the same dosage form, e.g. one

compound may be administered by injection and the other compound may be administered orally.

The compositions of this invention alleviate the symptoms associated with the disease state of benign prostatic hypertrophy to a greater extent than can be achieved by either component alone.

The claimed pharmaceutical compositions are incorporated into convenient dosage forms such as capsules, tablets, or injectable preparations. Solid or liquid pharmaceutical carriers are employed. Solid carriers include starch, lactose, calcium sulfate dihydrate, terra alba, sucrose, talc, gelatin, agar, pectin, acacia, magnesium stearate, and stearic acid. Liquid carriers include syrup, peanut oil, olive oil, saline, and water. Similarly, the carrier or diluent may include any prolonged release material, such as glyceryl monostearate or glyceryl distearate, alone or with a wax. The amount of solid carrier varies widely but, preferably, will be from about 25 mg to about 1 g per dosage unit. When a liquid carrier is used, the preparation will be in the form of a syrup, elixir, emulsion, soft gelatin capsule, sterile injectable liquid such as an ampoule, or an aqueous or nonaqueous liquid suspension.

The pharmaceutical preparations are made following conventional techniques of a pharmaceutical chemist involving mixing, granulating, and compressing, when necessary, for tablet forms, or mixing, filling and dissolving the ingredients, as appropriate, to give the desired oral or parenteral products.

The pharmaceutical properties of each active component of the pharmaceutical composition of the invention must be contemplated when formulating conventional dosage regimens. Both components can be incorporated into a timed release dosage unit form in which several doses are treated for delayed or sustained release of the medicament. Such dosage units may comprise sustained release granules, sugar centered spheres or multilayered tablets in each of which the availability of the active ingredient is controlled by coating with a lupid or polymeric material.

This invention also relates to a method of treating benign prostatic hypertrophy in a mammal, including a human, in need thereof which comprises administering N-t-butyl-androst-3,5-diene-17ß-carboxamide-3-carboxylic acid or a salt thereof or 17ß-(N-t-butylcarboxamide)-estra-

1,3,5(10)-triene-3-carboxylic acid or a salt thereof and an alpha-andrenergic receptor antagonist compound to such mammal.

Both prophylactic and therapeutic induction are contemplated. One of skill in the art will recognize that the exact dosage and treatment regimen to be utilized in any particular situation will necessarily depend on the exact disease state to be treated, the age, weight, sex and health of the particular animal being treated and that such optimums can be determined by conventional techniques.

To maximize its therapeutic effect, the individual compounds of the claimed combinations can be administered as a single pharmaceutical composition or consecutively in separate pharmaceutical compositions, whichever administration scheme may be appropriate. One of skill in the art using conventional techniques can determine the most appropriate way to administer the two compounds (consecutively versus simultaneously) depending on such factors as the age, sex weight and health of the patient and the disease state to be treated.

Doses of the present combination in a pharmaceutical dosage unit as described above will be an efficacious, non toxic quantity preferably selected from the range of 0.01-100 mg/kg of each active compound, preferably 0.1-50 mg/kg. The selected dose is administered to a patient in need of treatment for benign prostatic hypertrophy preferably from 1-6 times daily, orally, or parenterally. Preferred forms of parenteral administration include topically, rectally, transdermally, by injection and continuously by infusion. Oral dosage units for human administration preferably contain from 1 to 500 mg of active compound. Oral administration, which uses lower dosages is preferred. Parenteral administration, at high dosages, however, also can be used when safe and convenient for the patient.

No unacceptable toxicological effects are expected when compositions of the invention are administered in accordance with the present invention.

The use of a 5α-reductase inhibiting compound, other than compound A and compound B, in a pharmaceutical composition with an alpha-andrenergic receptor antagonist is contemplated. Persons skilled in the art can readily determine if a compound, other than compound A and compound B, is a 5α-reductase inhibiting compound by methods well

known in the art, such as those described in Levy et al: J. Steroid Biochem 34: 571-575, (1989). Thus, all such compounds are included within the scope of the term "5α-reductase inhibitor" as used herein.

The following examples illustrate preparation of the claimed pharmaceutical compositions. The examples are not intended to limit the scope of the invention as defined hereinabove and as claimed below.

EXAMPLE 1 - Gelatin Capsule

An oral dosage form for administering the claimed compounds and compositions is produced by screening, mixing and filling into hard gelatin capsules the ingredients in the proportions shown in Table I below.

Table I

Ingredients	Amounts
N-t-butyl-androst-3,5-diene-17ß-carboxamide-3-carboxylic acid	50 mg
Terazocin	50 mg
Magnesium stearate	10 mg
Lactose	150 mg

EXAMPLE 2 - Tablet

The lactose, microcrystalline cellulose and claimed compounds and compositions shown in Table II below, are mixed and granulated in the proportions shown with a 10% gelatin solution. The wet granules are screened, dried, mixed with the starch, talc and stearic acid, screened and compressed into a tablet.

Table II

Ingredients	Amounts
N-t-butyl-androst-3,5-diene-17ß-carboxamide-3-carboxylic acid	50 mg
Doxazosin	50 mg
Calcium sulfate dihydrate	75 mg
Sucrose	20 mg
Starch	10 mg
Talc	5 mg
Stearic acid	5 mg

EXAMPLE 3 - Injectable Preparation

N-t-butyl-androst-3,5-diene-17ß-carboxamide-3-carboxylic acid (50 mg) and amsulosin (50 mg), are dispersed in 25 ml of normal saline to prepare an injectable preparation.

EXAMPLE 4

The following compounds (expressed as base weight) are mixed together with 250 mg of lactose and 10 mg of magnesium stearate then filled into a hard gelatin capsule. These capsules are administered from 1-6 times daily to a patient in need of treatment of benign prostatic hypertrophy.

A. N-t-butyl-androst-3,5-diene-17ß-carboxamide-3-carboxylic acid 50 mg; prazosin 50 mg.

B. N-t-butyl-androst-3,5-diene-17ß-carboxamide-3-carboxylic acid 50 mg; alfuzosin 50 mg.

C. N-t-butyl-androst-3,5-diene-17ß-carboxamide-3-carboxylic acid 50 mg indoramin 50 mg.

While the preferred embodiments of the invention are illustrated by the above, it is to be understood that the invention is not limited to the precise instructions herein disclosed and that the right to all modifications coming within the scope of the following claims is reserved.

What is claimed is:

1. A pharmaceutical composition comprising a steroid 5-α-reductase inhibiting compound and an alpha-andrenergic receptor antagonist compound and a pharmaceutically acceptable carrier or diluent.

2. A pharmaceutical composition comprising N-t-butyl-androst-3,5-diene-17ß-carboxamide-3-carboxylic acid or a salt thereof and an alpha-andrenergic receptor antagonist compound and a pharmaceutically acceptable carrier or diluent.

3. A composition of claim 2 in which the alpha-andrenergic receptor antagonist is terazocin.

4. A composition of claim 2 in which the alpha-andrenergic receptor antagonist is selected from alfuzosin, indoramin, doxazosin, prazosin, amsulosin and 7-chloro-2-ethyl-3,4,5,6-tetrahydro-4-methylthieno[4,3,2-ef]-[3]benzazepine.

5. A composition according to anyone of claims 1 to 4 for use in therapy.

6. A composition according to anyone of claims 1 to 4 in the manufacture of a medicament for use as a steroid 5-α-reductase inhibitor.

7. A composition according to anyone of claims 1 to 4 in the manufacture of a medicament for use in treatment to reduce prostate size.

8. Use of a composition according to anyone of claims 1 to 4 in the manufacture of a medicament for use as a 5-α-reductase inhibitor.

9. The use of a steroid 5-α-reductase inhibiting compound and an alpha-receptor antagonist compound as an active therapeutic substance which use consist of separate sequential or simultaneous administration of a steroid 5-α-reductase inhibiting compound and an alpha-receptor antagonist compound.

10. The use of a steroid 5-α-reductase inhibiting compound and an alpha-receptor antagonist compound in the manufacture of a medicament for use in the treatment of benign prostatic hypertrophy which use consist of separate sequential or simultaneous administration of a 5-α-reductase inhibiting compound and an alpha receptor antagonist compound.

INTERNATIONAL SEARCH REPORT

PCT/US93/03145

A. CLASSIFICATION OF SUBJECT MATTER

IPC(5) :A61K 31/56
US CL :514/171
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/171 514/254,258,323,651

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US,A, 4,963,547 (Lafferty et al.) 16 October 1990 See the entire document.	1-10
Y	US,A, 5,017,568 (Holt et al.) 21 May 1991 See the entire document.	1-10

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
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Date of the actual completion of the international search 24 JUNE 1993	Date of mailing of the international search report 23 JUL 1993
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